

Novel cellular entities and their role in the etiopathogenesis of female idiopathic infertility—a review article

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DOI: [10.31083/j.ceog.2021.03.2395](https://doi.org/10.31083/j.ceog.2021.03.2395)

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Submitted: 3 December 2020 Revised: 1 February 2021 Accepted: 3 February 2021 Published: 15 June 2021

Background: Idiopathic or unexplained infertility is a broad subcategory of infertility defined by the absence of obvious or explainable cause, but accounts for at least 25% of all causes. Many possible hidden factors have been discussed over the years, but one of the most prominent and controversial players in this area recently, have been telocytes—newly discovered interstitial cells. Telocytes were first described only 15 years ago, but as of today, they have been observed in almost all organs of the human body including the uterine tubes, uterus and other organs of the female reproductive system. Aside from their vast array of physiological functions such as immune regulation, cell-to-cell signalling, cell-nursing and hormone-sensing, they have been also implicated in the pathogenesis of many different diseases, for which we have coined an original term “telocytopathies”. **Methods:** We have reviewed relevant articles in English on the topic of idiopathic infertility and telocytes mostly from the last 5 years, using PubMed/MEDLINE, Scopus and Web of Science databases. **Results:** Quantitative loss and functional derangement of telocytes may not cause any obvious pathological changes, but a subtle, yet important loss of crucial functions of telocytes can lead to unexplained infertility. **Discussion:** In the uterine tubes, possible mechanisms include changes in the structural and functional integrity of the cellular microenvironment. In the uterus, one of the main proposed mechanisms is immune dysregulation of macrophages and other immune cell populations. In the developing placenta, the main focus is placed on the role of telocytes in immune regulation and decidualisation. All these presupposed pathogenetic factors are still highly speculative, but possibly future research will elucidate the role of telocytes in these processes, which may lead to change of the status of idiopathic infertility, but also of many other “idiopathic” diseases regardless of the organ in question.

Keywords

Telocytes; Interstitial Cajal-like cells; Female infertility; Tubal transport function; Uterine telocytes; Hypotheses

1. Introduction

More than 300 years have passed since Antoni van Leeuwenhoek’s (1632–1723) breakthrough observations of bacteria and protozoa (“*animalcules*”) and various types of animal and human cells [1]. All these years of research have

brought an immensely deep understanding of the microscopic anatomy of the human body, which skyrocketed with the revolutionary invention of the electron microscope. This has resulted in a widespread opinion held by both scholars and lay public, that it is highly improbable to discover a new anatomical structure, tissue or cell population, especially in the 21st century. In spite of all that, a new cell population was indeed discovered only 15 years ago [2].

In 2005, a team of Romanian researchers under the leadership of Prof. Popescu (1944–2015) discovered a new cell type. At that time, they termed them interstitial Cajal-like cells, due to a presumable resemblance to pacemaker interstitial cells of Cajal located in the gut [2]. Five years later, these cells were renamed to telocytes. Although, their discovery was perceived as a case of serendipity, the authors remarked that, “chance only favours the prepared mind”, citing the famous Louis Pasteur [3]. Telocytes are a population of stromal (interstitial) cells, which occupy a wide variety of organs of the human body and many other *species*. They have been described in the heart [4], lungs [5], liver [6], kidney [7], gut [8], testes [9], as well as in almost all organs of the female reproductive system [10]. Regarding their functions, it is difficult to summarize them in a concise way. Telocytes have been described to perform many tasks in microenvironmental regulation, for instance immunomodulation, cell-to-cell signalling, tissue regeneration, to name but a few [11]. On the other hand, some scientists have not agreed to recognize telocytes as an individual cell population, but merely as a subtype of fibroblasts or a type of undifferentiated stem cells. This controversy is still actual regardless of the 400 and more papers, that have been published on the topic to this date. The *status quo* is best demonstrated by the absence of telocytes in any official morphological nomenclature, including *Terminologia Histologica* [12–14]. This discrepancy in opinions should be resolved as soon as possible, primarily because telocytes are not just “some” cells. They have been repeatedly implicated in the etiopathogenesis in many unrelated diseases in almost all organ systems of the human body. How-

ever, this topic is still controversial, same as the issue of their uniqueness as an individual cell population. Nevertheless, we were first to propose a new term “telocytopathies” [15], which demonstrates their potentially cardinal role in the development of a wide spectrum of diseases. The etiopathogenesis of some is obscured only partially, so perhaps telocytes will complete their understanding, but in the case of idiopathic diseases, telocytes have a potential to elucidate crucial aspects of the pathogenesis of these conditions what might be a game-changing moment in their comprehension.

The main aim of this review is to discuss this newly discovered cell population in selected organs of the female reproductive system in relation to female idiopathic infertility. We have reviewed relevant articles in English on the topic mostly from the last 5 years, using PubMed/MEDLINE, Scopus and Web of Science databases.

2. Telocytes and female infertility

2.1 Telocytes in the female reproductive system

From the morphological perspective, telocytes can be best characterised as cells with telopodes [16]. Telopodes are very long cytoplasmic projections, but their width is only around the resolving power of the light microscope [17]. This is probably the reason for their late discovery. Using these projections, telocytes form a three-dimensional network in the interstitium which connects many different stromal cells and other components, like different populations of immune cells, blood vessels, nerve fibres and glands [18]. Edelstyn and Smithies [19] described this overly complicated network as a cellular-level counterpart of the nervous system. Telocytes have been thoroughly documented in most organs of the female reproductive system. They have been studied in the vagina (regulation of smooth muscle contractility) [20], mammary gland (functional regulation, immunomodulation, and possible role in carcinogenesis) [21], or even placenta (role in the pathogenesis of preeclampsia) [22]. In regard to female infertility, researchers have focused on many different organs of the female reproductive system. For instance, diminished count of ovarian telocytes has been observed in patients with premature ovarian failure, a condition characterised by untimely stoppage of normal ovarian function, often leading to infertility [23]. In the following paragraphs, we will focus on telocytes and their relation to infertility in the uterine tubes, uterus and developing placenta.

2.2 Female infertility

Infertility as a disease entity is established when a couple is unable to conceive a child despite having regular unprotected coitus for over a year. This condition affects around 8–12% of couples around the globe [24]. The most recent estimates are even higher. According to the European Society of Human Reproduction and Embryology (ESHRE), the incidence of infertility can reach 15% [25]. There are many causes, which can be attributed solely to female, solely to male, to combined factors of both sexes and finally yet importantly, there is also a broad category of unexplained or idiopathic

infertility without any obvious or explainable cause. It accounts for about 25–30% of all cases [26]. The female factors include dysfunction of the menstrual cycle, ovulation, as well as various conditions that affect the uterine tubes and uterus [27]. Others include post-infectious changes after the recovery from, e.g., *Chlamydia trachomatis* infection, or rare conditions such as congenital bilateral agenesis of the uterine tubes [28]. These factors are well researched and understood as causative determinants of infertility. On the other hand, unexplained (idiopathic) infertility can be caused by either various vaguely defined psychological factors, perhaps related to depression or stress [29], or somatic changes in an individual organ of the female reproductive system, which are delicate and thus hard to notice by common diagnostic methods [30].

2.3 Tubal telocytes and female infertility

Tubal telocytes have many possible functions, but one of the most commonly reported is their ability to “sense” the levels of female sex hormones and thus regulate those processes inside the uterine tubes, which are under hormonal control. This function is implied by telocytes expression of oestrogen and progesterone receptors [31]. Most of the functions of the uterine tubes related to fertility are hormonally regulated, from oocyte pick-up by *fimbriae*, through sperm migration, to early embryo nourishment. Telocytes also affect smooth muscle contractility, functioning as “pacemakers” [32]. One of the most discussed roles of telocytes is their ability to mediate intercellular signalling between various stromal, as well as parenchymal components. They have been repeatedly observed in morphological studies to make cell-to-cell contacts with blood vessels, nerve fibres, glandular epithelial cells [33], but also very importantly, with various populations of immune cells belonging to both the innate and adaptive immune system. This immunomodulatory function has been attributed to telocytes in almost all the organs in which they have been studied, regardless of a particular organ system [34]. The principal observed pathological change of telocytes is their quantitative reduction and/or functional alteration. However, it is far from resolved, whether these changes are primary, or only secondary to the overall damage of the disease-affected tissue. Interestingly, Yang *et al.* [35] performed an experimental study, utilizing a rat oviduct model of acute salpingitis, in which the authors described for the first time, that telocytes were functionally and morphologically damaged and also reduced in number. This finding was classic and not very surprising. Strikingly though, the authors also proposed a possibility, that interstitial fibrosis observed in their animal model was directly caused by telocytes damage, not the other way around. The study also implicated that telocytes might be involved in immune-mediated early pregnancy failure [35]. It is long known that a highly complex immune regulation is important in every step of successful gestation. If there is any problem in the finely orchestrated interplay of immune responses, it can result in major pathological changes in any organ involved in the conception and gestation, including the uterine tubes. These clearly observ-

able changes would account for well-known causes of female infertility. On the other hand, the changes don't have to be well pronounced necessarily. Some might be very delicate, without any straightforward histopathological findings, yet capable of causing infertility. These would lead to the diagnosis of idiopathic/unexplained infertility. There are many possible mechanisms of how this dysregulation might come about, however the definitive answers are still out of reach [36]. We think, that telocytes are possibly the answer in this setting, but more experimental studies are needed in order to find out, whether this line of thought is plausible or otherwise. In order for this to be fulfilled, we hold an opinion that telocytes should be scrutinised in most pathophysiological processes related to tubal factor infertility, especially in those which are not completely understood like endometriosis. This approach will bring more knowledge on the role of telocytes in various pathological processes of the uterine tubes, what in turn may bring a better understanding of their role in infertility.

2.4 Uterine telocytes and female infertility

Telocytes inside the uterus are well documented in the literature. The first paper focusing on uterine telocytes was published shortly after telocytes were discovered themselves [37]. In 2015, Roatesi *et al.* authored a comprehensive review of uterine telocytes, summarizing a significantly large body of knowledge obtained over the course of 10 years from their initial description. Well documented in the endometrium as well as the myometrium, telocytes were reviewed to be involved in such processes as endometrial maintenance, myometrial contractility, intercellular signalling, uterine regeneration and renewal, mechanoreception, hormone-sensing, pacemaking, contractility modulation, and finally immune surveillance [38]. Considering this multitude of different functions, it is not surprising that telocytes have also been described in various uterine pathologies related to infertility. One such condition which has been studied extensively is the role of telocytes in the development of benign smooth muscle neoplasms, commonly referred to as leiomyomas or fibroids [39]. Although their exact effect on fertility is equivocal, it has been repeatedly reported, that uterine fibroids may impair fertility rates depending upon their location [40]. The role of telocytes in the pathogenesis of this condition has been previously reported by us as well as other authors. Our immunohistochemical findings were quite surprising—the whole leiomyoma tissue was utterly devoid of telocytes. We proposed three hypotheses, which could possibly elucidate the role of telocytes in the leiomyoma formation. The loss of telocytes possibly leads to dysregulation of hormonal balance, diminished formation of new blood vessels, and also disbalance of uterine stem cells. These are all processes which may trigger the neoplasm formation [39]. A recent paper by Aleksandrovych *et al.* [41] reviewed the role of telocytes in different aspects of leiomyoma pathogenesis, mainly how the loss of telocytes affects the normal tissue organisation, regulation of extracellular matrix production, vascularisation

and stem cell nursing. With regard to idiopathic infertility, similarly to tubal telocytes, uterine telocytes are also involved in immune regulation and surveillance. However, so far as uterine tubes are concerned, they are necessary for successful development of an early embryo in the first days after conception. However, a uterus has to function properly from the implantation by the end of the first week of development, until labour. This temporal aspect implies that the proper regulation of uterine functions can be even more intricate. There are multiple studies, which discussed the possible influence of telocytes on various populations of immune cells. Telocytes were experimentally demonstrated to “educate” macrophages, which are important mediators of the local microenvironment of immune cells in the interstitium of different organs. Even though, this study focused on peritoneal macrophages [42], future studies might demonstrate a possible applicability of these results also to other populations of macrophages, including those located in the uterine stroma.

2.5 Placental telocytes and female infertility

Placenta is a transient organ vital for proper development of the embryo, as well as the foetus. Its formation requires a highly elaborate interaction between embryonic/foetal and maternal tissues, has a very specific blood supply, provides nutrition, exchanges breathing gases and also excretes waste substances, so it substitutes those functions which are normally provided by the lungs, gut and kidneys. Placenta is also a highly active endocrine organ [43]. Placenta contains many different populations of immune cells, which are relevant in many physiological functions as well as pathological states [44]. Placental telocytes have been previously studied, although not as extensively as in the uterine tubes and uterus. Nevertheless, their potential roles in placental physiology and also in various pathological conditions are remarkable. They have been observed to occupy strategic position between smooth muscle cells of the foetal blood vessels and myofibroblasts of the stroma [45]. According to experimental observations, placental telocytes are also significant in the regulation of placental immune cells. Telocytes were observed electron microscopically, to form a network in close vicinity of Hofbauer cells - macrophages of the placental villi important for placenta development, homeostasis and protection from being rejected by the maternal immune system [46]. A possible influence of telocytes on placental functions can be relevant also in other pregnancy-related pathologies such as preeclampsia, as briefly mentioned earlier [22]. The proper development of the maternal part of the placenta is impossible without specific changes in the endometrial stroma, called decidual reaction. A part of the reaction is the differentiation of stromal fibroblasts to decidual cells [47]. With regard to telocytes, Tang *et al.* [48] cultivated telocytes *in vitro* with stromal cells obtained from the endometrium. The authors observed that telocytes interacted with the stromal cells and increased their capacity for migration, proliferation, and adhesion. Although the mentioned study didn't focus on the

infertility issue, these observations are significant in this regard, because deficient decidualisation may cause infertility [49] which is difficult to manage. A possible future avenue is the transplantation of telocytes, which has been previously attempted in an animal study using the model of renal fibrosis with promising results [50].

3. Conclusions and future perspectives

The role of telocytes in the etiopathogenesis of different diseases is intriguing, but still highly speculative. For some researchers, it is difficult to imagine a possibility that a single cell population can have such a massive impact on the proper functioning of so many different organs. “Telocytopathies” as an umbrella concept representing all the diseases, which develop because of the telocytes derangement is controversial, but also potentially ground-breaking. Only future research endeavours of telocytes will show, whether these considerations were a blunder, or a game-changing moment in thorough understanding of those diseases, whose etiopathogenesis has been understood only partially, or not at all. In the case of idiopathic conditions, including idiopathic infertility, telocytes may change the way how we look at them, and also significantly improve therapeutic strategies. A future perspective is the change of the status of idiopathic infertility, but also other idiopathic conditions. The proper understanding of any disease widens the frontiers of biomedical sciences, but most importantly, it is beneficial for a patient, because the elucidation of etiopathogenesis equals better diagnostics and therapy.

Abbreviations

ESHRE, European Society of Human Reproduction and Embryology.

Author contributions

IV had the idea for the article and critically revised the work. MK, LL and DF performed the literature search and drafted the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This study was supported by grants from the Slovak Research and Development Agency grant number APVV-18-0499.

Conflict of interest

The authors declare no conflict of interest.

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